PATENT COOPERATION TREAT

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
VS:WSWS:FP13136		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/AU00/00886	21 July 2000	23 July 1999

Applicant

THE UNIVERSITY OF MELBOURNE et al

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of **5** sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing.

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (See Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure

[ ] because this figure better characterizes the invention

[X] None of the figures

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00886

Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos : **41**

because they relate to subject matter not required to be searched by this Authority, namely:

This claim is to a method of treatment. Under rule 67.1 of the PCT this is excluded subject matter. However the search has been carried out based on the effects of the compound or pharmaceutical composition.

2. [X] Claims Nos : **1-21**

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

A full search was not possible on economic grounds. Claim 1 is inadequately defined. The documents cited are only a sample of possible compounds, including known compounds as described in the specification which inherently possess the properties as claimed in claim 1.

3. [ ] Claims Nos :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00886

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7] C07D 487/22, 257/02, C07K 7/06, 14/47, 14/795, A61K 38/08, 38/41, A61P 25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Database: STN, Files: CA, Medline, Biosis, WPIDS. Key words: beta amyloid, amyloid beta protein or peptide, abeta, N-term?, His 6, 13 or 14, inhib?, block?, destab?, compet? or bind?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Biochemistry, volume 39, 2000, pages 7024-7031, T. Miura et al, "Metal binding modes of Alzheimer's amyloid β-peptide in insoluble aggregates and soluble complexes." Entire document.	1-42
X	Journal of Biological Chemistry, volume 273, no. 21, 1998, pages 12817-12826, C.S. Atwood et al, "Dramatic aggregation of Alzheimer Aβ by Cu(II) is induced by conditions representing physiological acidosis." Entire document and abstract.	1-42
X	Alzheimer's Research, volume 2, 1996, pages 189-194, L.J. Bartolotti et al, "A model for the tertiary structure of the β-amyloid peptide." See especially page 192, third paragraph.	1-42

[X] Further documents are listed in the continuation of Box C [ ] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 2000	- 6 SEP 2000

Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Frances Roden **FRANCES RODEN** Telephone No : (02) 6283 2239

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00886

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5958883 (Board of Regents of the University of Washington Office of Technology), 28 September 1999. Entire document, especially column 15 lines 60-66.	1-21
X	WO 95/12815 (The Research Foundation of State University of New York), 11 May 1995. Entire document, especially claim 2.	1-21
X	Chemical Abstracts 85:28019 & J. Chem. Soc., Dalton Transactions, 1976, no. 10, pages 858-862, P-K Chan et al, "Structural and mechanistic studies of coordination compounds. Part XIII. Syntheses and characterization of some dianiono(1,4,8,11-tetraazacyclotetradecane)manganese(III), -iron(III), and -nickel(III) salts. See abstract.	1-21
X	Journal of Molecular Biology, volume 285, January, 1999, pages 755-773, H. Shao et al, "Solution structures of micelle-bound amyloid β-(1-40) and β-(1-42) peptides of Alzheimer's disease." See page 767, left column, lines 54-60.	1-21
X	Journal of Neuroimmunology, volume 95, March, 1999, pages 136-142, D. Frenkel et al, "High affinity binding of monoclonal antibodies to the sequential epitope EFRH of β-amyloid peptide is essential for modulation of fibrillar aggregation." Entire document, especially page 141, second paragraph.	1-21
X	Journal of Biological Chemistry, volume 273, no. 13, 1998, pages 7185-7188, M. Pappolla et al, "Inhibition of Alzheimer β-fibrillogenesis by Melatonin." Entire document.	1-21
X	WO 98/44955 (Mindset Ltd.), 15 October 1998. See especially claim 1.	1-21
A	Biochemistry, volume 33, 1994, pages 7788-7796, J. Talafous et al, "Solution structure of residues 1-28 of the Amyloid β-peptide." Entire document, especially figure 3.	1-42
A	Journal of Biological Chemistry, volume 273, no. 45, 1998, pages 29719-29726, D. Giulian et al, "The HHQK domain of β-amyloid provides a structural basis for the immunopathology of Alzheimer's disease." Entire document.	1-42

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU00/00886

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	98/44955	AU	71034/98	CN	1254294	EP	994728
WO	95/12815	AU	81310/94	US	5744368		

END OF ANNEX

PATENT COOPERATION TREAT

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GRIFFITH HACK
GPO Box 1285K
MELBOURNE VIC 3001

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	23 MAR 2001
Applicant's or agent's file reference VS:F:FP13136	**REPLY DUE** within **TWO MONTHS** from the above date of mailing

International Application No.	International Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU00/00886	21 July 2000	23 July 1999

International Patent Classification (IPC) or both national classification and IPC
Int. Cl. [7] C07D 487/22, 257/02, C07K 7/06, 14/47, 14/795, A61K 38/08, A61P 25/28

Applicant

THE UNIVERSITY OF MELBOURNE et al

1. This written opinion is the **first** drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:.

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: **23 November 2001**

Name and mailing address of the IPEA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
E-mail address: pct@ipaustralia.gov.au
Facsimile No. (02) 6285 3929

Authorized Officer

FRANCES RODEN
Telephone No. (02) 6283 2239

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

- [X] the international application as originally filed.
- [ ] the description, pages , as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [ ] the claims, pages , as originally filed,
  pages , as amended under Article 19,
  pages , filed with the demand,
  pages , received on with the letter of
- [ ] the drawings, pages , as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [ ] the sequence listing part of the description:
  pages , as originally filed
  pages , filed with the demand
  pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

- [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- [ ] the language of publication of the international application (under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- [ ] contained in the international application in printed form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form.
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages
   - [ ] the claims, Nos.
   - [ ] the drawings, sheets/fig.

5. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**2-42**	**YES**
	Claims	**1**	**NO**
Inventive step (IS)	Claims	**2, 6-10, 12-21, 25-28, 35-40**	**YES**
	Claims	**1, 3-5, 11, 22-24, 29-34, 41, 42**	**NO**
Industrial applicability (IA)	Claims	**1-42**	**YES**
	Claims		**NO**

2. Citations and explanations

The following documents cited in the ISR have been considered:

1. Journal of Biological Chemistry, vol. 273, 1998, pages 12817-12826, C. S. Atwood et al
2. Alzheimer's Research, vol. 2, 1996, pages 189-194, L. J. Bartolotti et al
3. US 5958883
4. WO 95/12815
5. Chemical Abstracts 85:28019
6. Journal of Molecular Biology, vol. 285, 1999, pages 755-773, H. Shao et al
7. Journal of Neuroimmunology, vol. 95, 1999, pages 136-142, K. Frenkel et al
8. Journal of Biological Chemistry, vol. 273, 1998, pages 7185-7188, M. Pappolla et al
9. WO 98/44955

Citation 1

Claims 1, 4, 5, 11, 22-24, 29-31, 33, 34, 41 and 42 do not contain an inventive step in light of this citation. Cortical deposition and aggregation of Aβ occurs in Alzheimer's disease. This document teaches that zinc and copper ions aggregate Aβ and that aggregation decreases if the histidine residues are modified. It teaches that histidine residues are essential for metal-mediated Aβ aggregation. It would therefore be obvious to a person skilled in the art to block histidines in Aβ to decrease aggregation thereby treating, preventing or alleviating Alzheimer's disease. Methods of selecting or designing compounds to block histidines in Aβ involve standard procedures that a person skilled in the art would be able to perform without having to overcome any major problems or difficulties. The above claims do not identify the metal-binding site, ie the specific histidine residues of Aβ that may be used as targets for potential therapeutic agents.

Citation 2

Claims 1,3-5, 11,22-24, 29-34, 41, 42 do not contain an inventive step in light of this citation. This document discloses a model for a zinc-bound form of Aβ. The zinc is found to bind at amino acids 20-22. Page 192 states that long-range interactions exist between Glu-22 and His-13 or His-14. This interaction leads the authors to predict the structure of an aggregated Aβ. Given this citation, it would have been obvious for a

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 9 is appended to itself, it appears as if it should be appended to claim 8.

Claim 41 is to a method of treatment. Under rule 67.1 of the PCT this is excluded subject matter, however as this claim does not contravene Australian law it has been examined.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V

person skilled in the art to block the His-13 and/or His-14 residues in order to decrease or eliminate zinc binding, thereby decreasing Aβ aggregation. Designing compounds to perform this function involve standard procedures that a person skilled in the art would be able to perform without having to overcome any major problems or difficulties.

Citation 3

Claim 1 is not novel in light of this citation. This document discloses at column 15 lines 60-66, a six amino acid peptide that binds to residues 12-17 of the β-amyloid peptide. This peptide will thus inherently inhibit the binding of one or more metal ions to a histidine in this region.

Citation 4

Claim 1 is not novel in light of this citation. This citation discloses a binding surface on Aβ which may be used for drug design, this surface includes His13. One compound proposed to prevent Aβ aggregation is transthyretin. This compound binding at the N-terminal loop of the β-amyloid peptide will inherently inhibit metal ions from binding and therefore renders claim 1 not novel.

Citation 5

Claim 1 is not novel in light of this citation. This citation discloses the synthesis of metallo-macrocyclic compounds. The compounds per se are known and they inherently perform the blocking/destabilising of the N-terminal loop of Aβ, thus inhibiting the binding of one or more metal ions, as claimed in claim 1.

Citation 6

Claim 1 is not novel in light of this citation. Page 767, left hand side, last 8 lines states that nicotine binds to the His13 and His14 of Aβ , preventing β-amyloid precipitation. In this situation the nicotine is binding at the N-terminal loop and inherently is inhibiting the binding of one or more metal ions, thus rendering claim 1 not novel.

Citation 7

Claim 1 is not novel in light of this citation. Page 141 paragraph 2 discloses antibodies which bind at the N-terminus of Aβ, including His6. These compounds therefore inherently inhibit the binding of one or more metal ions at this site.

Citation 8

Claim 1 is not novel in light of this citation. This document discloses that melatonin inhibits Aβ aggregation through binding at the N-terminus of the peptide. The binding site is disclosed to involve the three His and Asp residues. Melatonin will therefore inherently inhibit metal ions from binding within the N-terminal loop. This citation therefore contains all the essential features of claim 1.

Citation 9

Claim 1 is not novel in light of this citation. This citation discloses antibodies that bind specifically to the N-terminus of Aβ. These compounds therefore inherently block the binding of one or more metal ions at this site.

Citations 3-10 disclose compounds per se which fall within the scope of claim 1. These compounds all interact with the N-terminal loop of the β-amyloid peptide (binding at one or all of His6, His13 and His14) and they therefore inherently inhibit the binding of one or more metal ions to at least one histidine residue within the N-terminal loop. The specific metal-ion binding site containing the 3 histidine residues His 6, His13 and His 14 is not claimed in claim 1. Neither is the fact that the inhibition of this site may help prevent Aβ aggregation. The methods to select or design the compounds as claimed in claims 22 and 31 are not disclosed or suggested in the above citations.

PATENT COOPERATION TREA

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GRIFFITH HACK
GPO Box 1285K
MELBOURNE VIC 3001

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	11 AUG 2001
Applicant's or agent's file reference VS:F:FP13136	**REPLY DUE** within **ONE MONTH** from the above date of mailing

International Application No.	International Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU00/00886	21 July 2000	23 July 1999

International Patent Classification (IPC) or both national classification and IPC
Int. Cl. [7] C07D 487/22, 257/02, C07K 7/06, 14/47, 14/795, A61K 38/08, A61P 25/28

Applicant

THE UNIVERSITY OF MELBOURNE et al

1. This written opinion is the **second** drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:.

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: **23 November 2001**

Name and mailing address of the IPEA/AU	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	**FRANCES RODEN** Telephone No. (02) 6283 2239

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1,2,4-40,** as originally filed,
pages , filed with the demand,
pages **3,** received on **25 July 2001** with the letter of **23 July 2001**

☒ the claims, pages **41,44,45** as originally filed,
pages , as amended under Article 19,
pages , filed with the demand,
pages **42,43,** received on **25 July 2001** with the letter of **23 July 2001**

☒ the drawings, pages **1/10-10/10,** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**1-42**	**YES**
	Claims		**NO**
Inventive step (IS)	Claims	**2, 3, 6-10, 12-21, 25-28, 32,35-40**	**YES**
	Claims	**1, 4, 5, 11, 22-24, 29-31, 33, 34, 41, 42**	**NO**
Industrial applicability (IA)	Claims	**1-42**	**YES**
	Claims		**NO**

2. Citations and explanations

The following documents cited in the ISR have been considered:

1. Journal of Biological Chemistry, vol. 273, 1998, pages 12817-12826, C. S. Atwood et al
2. Alzheimer's Research, vol. 2, 1996, pages 189-194, L. J. Bartolotti et al
3. US 5958883
4. WO 95/12815
5. Chemical Abstracts 85:28019
6. Journal of Molecular Biology, vol. 285, 1999, pages 755-773, H. Shao et al
7. Journal of Neuroimmunology, vol. 95, 1999, pages 136-142, K. Frenkel et al
8. Journal of Biological Chemistry, vol. 273, 1998, pages 7185-7188, M. Pappolla et al
9. WO 98/44955

Citation 1

Claims 1, 4, 5, 11, 22-24, 29-31, 33, 34, 41 and 42 do not contain an inventive step in light of this citation. Cortical deposition and aggregation of Aβ occurs in Alzheimer's disease. This document teaches that zinc and copper ions aggregate Aβ and that aggregation decreases if the histidine residues are modified. It teaches that histidine residues in the N-terminus are essential for metal-mediated Aβ aggregation. Given this information it would be obvious to a person skilled in the art to either block the N-terminal histidines in Aβ, thus preventing metal ions from binding, thereby decreasing aggregation and thus treating, preventing or alleviating Alzheimer's disease; or to delete or modify the histidine residues such that a conformational change in the peptide prevents metal-mediated aggregation. Either of these options would be obvious to a person skilled in the art to try. Methods of selecting or designing compounds to block histidines in Aβ involve standard procedures that a person skilled in the art would be able to perform without having to overcome any major problems or difficulties. Once at least one of the histidine residues is blocked by a compound then metal ion binding at this site will be prevented.

An inventive step can be acknowledged for claim 2 as it would not be possible to predict which compounds would inhibit the binding of copper, zinc and iron, but not magnesium or calcium. Claim 3 contains an inventive step as the citation does not teach the specific histidine residues in the N-terminal region at which metal binding is inhibited. Claims 6-10, 12-21, 25-28, 32, and 35-40 are inventive as they contain features that would not be obvious to a person skilled in the art given the information in this citation.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 41 is to a method of treatment. Under rule 67.1 of the PCT this is excluded subject matter, however as this claim does not contravene Australian law it has been examined.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V

Citation 2

The claims are novel and inventive in light of this citation. A theoretical model for a zinc-bound form of Aβ is disclosed in which the zinc binds at amino acids 20-22. Long-range interactions between Glu-22 and His-13 or His-14 are disclosed, however these interactions assist in dimer and higher oligomer formation and do not appear to be related to Aβ metal binding.

Citation 3

The claims are novel and inventive in light of this citation. This document discloses a six amino acid peptide that competes with the heparin-binding site of Aβ, it does not bind to the amyloid peptide itself and will therefore not inhibit the binding of one or more metal ions to an N-terminal histidine of β-amyloid peptide.

Citation 4

The claims are novel and inventive in light of this document. This citation discloses a binding surface on Aβ which may be used for drug design, this surface encompasses the residue His13. One compound proposed to prevent Aβ aggregation is transthyretin. The citation does not disclose that transthyretin specifically binds to His 13, therefore it is not necessarily inherent that the binding of transthyretin would inhibit the binding of one or more metal ions to this particular histidine residue.

Citation 5

The claims are novel and inventive in light of this citation. The citation discloses the synthesis of known metallo-macrocyclic compounds, which are described in the admitted prior art of the present application. However the citation does not teach or suggest that these compounds bind to a histidine residue within the N-terminal loop of Aβ, it would therefore not be possible for a person skilled in the art to predict that these compounds would prevent a metal ion from binding specifically to a histidine residue in this region.

Citation 6

The claims are novel and inventive in light of this citation. Page 767, left hand side, last 8 lines states that nicotine binds to the His13 and His14 of Aβ , preventing β-amyloid precipitation. The binding of nicotine to these histidine residues is likely to be relatively weak and it would therefore be unlikely to compete with metal ion binding to these sites. Without evidence to the contrary, it would therefore appear that nicotine would not act as a compound that would inhibit the binding of one or more metal ions to at least one histidine residue within the N-terminal loop of the β-amyloid peptide and therefore the claims are novel and inventive.

Citation 7

The claims are novel and inventive in light of this citation. Page 141 paragraph 2 discloses antibodies which bind at the N-terminus of Aβ. It does not however disclose that these synthetic antibodies specifically bind at the His6 site and it cannot therefore be said that a metal ion would definitely be inhibited from binding at this histidine residue.

Citation 8

The claims are novel and inventive in light of this citation. This document discloses that melatonin inhibits Aβ aggregation through binding at the N-terminus of the peptide. The binding site is disclosed to directly involve His6, 13 and 14 and an Asp residue. However there is no evidence in this citation that melatonin would bind strongly enough to prevent metal ions from binding at the histidine residues, or that melatonin would displace metal ions already bound at the N-terminal loop. Without evidence to the contrary, it would appear that melatonin would not necessarily bind to at least one histidine residue in the N-terminal loop of Aβ such that the binding of one or more metal ions is inhibited.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V

Citation 9

The claims are novel and inventive in light of this citation. This citation discloses antibodies that bind to the N-terminus of Aβ. It does not however disclose that these antibodies specifically bind to at least one histidine residue within the N-terminus. It cannot therefore be said that these antibodies would inherently inhibit the binding of one or more metal ions to one of the N-terminal loop histidine residues.

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GRIFFITH HACK
GPO Box 1285K
MELBOURNE VIC 3001

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *day/month/year* - 9 OCT 2001

Applicant's or agent's file reference
VS:F:fp13136

IMPORTANT NOTIFICATION

International Application No.	International Filing Date	Priority Date
PCT/AU00/00886	21 July 2000	23 July 1999

Applicant
THE UNIVERSITY OF MELBOURNE et al

1 The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.

4 **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

Name and mailing address of the IPEA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	FRANCES RODEN Telephone No. (02) 6283 2239

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference VS:F:fp13136	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU00/00886**	International Filing Date *(day/month/year)* 21 July 2000	Priority Date *(day/month/year)* 23 July 1999
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] C07D 487/22, 257/02, C07K 7/06, 14/47, 14/795, A61K 38/08, A61P 25/28		
Applicant THE UNIVERSITY OF MELBOURNE et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
19 February 2001	4 October 2001
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **FRANCES RODEN** Telephone No. (02) 6283 2239

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU00/00886

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1,2,4-40,** as originally filed,
pages , filed with the demand,
pages **3,** received on **25 July 2001** with the letter of **23 July 2001**

☒ the claims, pages **41,44,45,** as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **42,43,** received on **25 July 2001** with the letter of **23 July 2001**

☒ the drawings, pages **1/10-10/10,** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**1-42**	**YES**
	Claims		**NO**
Inventive step (IS)	Claims	**2, 3, 6-10, 12-21, 25-28, 32, 35-40**	**YES**
	Claims	**1, 4, 5, 11, 22-24, 29-31, 33, 34, 41, 42**	**NO**
Industrial applicability (IA)	Claims	**1-42**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

The following documents cited in the ISR have been considered:

1. Journal of Biological Chemistry, vol. 273, 1998, pages 12817-12826, C. S. Atwood et al
2. Alzheimer's Research, vol. 2, 1996, pages 189-194, L. J. Bartolotti et al
3. US 5958883
4. WO 95/12815
5. Chemical Abstracts 85:28019
6. Journal of Molecular Biology, vol. 285, 1999, pages 755-773, H. Shao et al
7. Journal of Neuroimmunology, vol. 95, 1999, pages 136-142, K. Frenkel et al
8. Journal of Biological Chemistry, vol. 273, 1998, pages 7185-7188, M. Pappolla et al
9. WO 98/44955

Citation 1

Claims 1, 4, 5, 11, 22-24, 29-31, 33, 34, 41 and 42 do not contain an inventive step in light of this citation. Cortical deposition and aggregation of Aβ occurs in Alzheimer's disease. This document teaches that zinc and copper ions aggregate Aβ and that aggregation decreases if the histidine residues are modified. It teaches that histidine residues in the N-terminus are essential for metal-mediated Aβ aggregation. Given this information it would be obvious to a person skilled in the art to either block the N-terminal histidines in Aβ, thus preventing metal ions from binding, thereby decreasing aggregation and thus treating, preventing or alleviating Alzheimer's disease; or to delete or modify the histidine residues such that a conformational change in the peptide prevents metal-mediated aggregation. Either of these options would be obvious to a person skilled in the art to try. Methods of selecting or designing compounds to block histidines in Aβ involve standard procedures that a person skilled in the art would be able to perform without having to overcome any major problems or difficulties. Once at least one of the histidine residues is blocked by a compound then metal ion binding at this site will be prevented.

An inventive step can be acknowledged for claim 2 as it would not be possible to predict which compounds would inhibit the binding of copper, zinc and iron, but not magnesium or calcium. Claim 3 contains an inventive step as the citation does not teach the specific histidine residues in the N-terminal region at which metal binding is inhibited. Claims 6-10, 12-21, 25-28, 32, and 35-40 are inventive as they contain features that would not be obvious to a person skilled in the art given the information in this citation.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 41 is to a method of treatment. Under rule 67.1 of the PCT this is excluded subject matter, however as this claim does not contravene Australian law it has been examined.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V

Citation 2

The claims are novel and inventive in light of this citation. A theoretical model for a zinc-bound form of Aβ is disclosed in which the zinc binds at amino acids 20-22. Long-range interactions between Glu-22 and His-13 or His-14 are disclosed, however these interactions assist in dimer and higher oligomer formation and do not appear to be related to Aβ metal binding.

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The claims are novel and inventive in light of this citation. This document discloses a six amino acid peptide that competes with the heparin-binding site of Aβ, it does not bind to the amyloid peptide itself and will therefore not inhibit the binding of one or more metal ions to an N-terminal histidine of β-amyloid peptide.

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Citation 6

The claims are novel and inventive in light of this citation. Page 767, left hand side, last 8 lines states that nicotine binds to the His13 and His14 of Aβ , preventing β-amyloid precipitation. The binding of nicotine to these histidine residues is likely to be relatively weak and it would therefore be unlikely to compete with metal ion binding to these sites. Without evidence to the contrary, it would therefore appear that nicotine would not act as a compound that would inhibit the binding of one or more metal ions to at least one histidine residue within the N-terminal loop of the β-amyloid peptide and therefore the claims are novel and inventive.

Citation 7

The claims are novel and inventive in light of this citation. Page 141 paragraph 2 discloses antibodies which bind at the N-terminus of Aβ. It does not however disclose that these synthetic antibodies specifically bind at the His6 site and it cannot therefore be said that a metal ion would definitely be inhibited from binding at this histidine residue.

Citation 8

The claims are novel and inventive in light of this citation. This document discloses that melatonin inhibits Aβ aggregation through binding at the N-terminus of the peptide. The binding site is disclosed to directly involve His6, 13 and 14 and an Asp residue. However there is no evidence in this citation that melatonin would bind strongly enough to prevent metal ions from binding at the histidine residues, or that melatonin would displace metal ions already bound at the N-terminal loop. Without evidence to the contrary, it would appear that melatonin would not necessarily bind to at least one histidine residue in the N-terminal loop of Aβ such that the binding of one or more metal ions is inhibited.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V

Citation 9

The claims are novel and inventive in light of this citation. This citation discloses antibodies that bind to the N-terminus of Aβ. It does not however disclose that these antibodies specifically bind to at least one histidine residue within the N-terminus. It cannot therefore be said that these antibodies would inherently inhibit the binding of one or more metal ions to one of the N-terminal loop histidine residues.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference VS:F:fp13136	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU00/00886**	International Filing Date *(day/month/year)* 21 July 2000	Priority Date *(day/month/year)* 23 July 1999
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] C07D 487/22, 257/02, C07K 7/06, 14/47, 14/795, A61K 38/08, A61P 25/28		
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VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

Date of submission of the demand 19 February 2001	Date of completion of the report 4 October 2001
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **FRANCES RODEN** Telephone No. (02) 6283 2239

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU00/00886

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pages , as originally filed
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1. Statement

Novelty (N)	Claims	1-42	YES
	Claims		NO
Inventive step (IS)	Claims	2, 3, 6-10, 12-21, 25-28, 32, 35-40	YES
	Claims	1, 4, 5, 11, 22-24, 29-31, 33, 34, 41, 42	NO
Industrial applicability (IA)	Claims	1-42	YES
	Claims		NO

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2. Alzheimer's Research, vol. 2, 1996, pages 189-194, L. J. Bartolotti et al
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Claim 41 is to a method of treatment. Under rule 67.1 of the PCT this is excluded subject matter, however as this claim does not contravene Australian law it has been examined.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V

Citation 2

The claims are novel and inventive in light of this citation. A theoretical model for a zinc-bound form of Aβ is disclosed in which the zinc binds at amino acids 20-22. Long-range interactions between Glu-22 and His-13 or His-14 are disclosed, however these interactions assist in dimer and higher oligomer formation and do not appear to be related to Aβ metal binding.

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Citation 4

The claims are novel and inventive in light of this document. This citation discloses a binding surface on Aβ which may be used for drug design, this surface encompasses the residue His13. One compound proposed to prevent Aβ aggregation is transthyretin. The citation does not disclose that transthyretin specifically binds to His 13, therefore it is not necessarily inherent that the binding of transthyretin would inhibit the binding of one or more metal ions to this particular histidine residue.

Citation 5

The claims are novel and inventive in light of this citation. The citation discloses the synthesis of known metallo-macrocyclic compounds, which are described in the admitted prior art of the present application. However the citation does not teach or suggest that these compounds bind to a histidine residue within the N-terminal loop of Aβ, it would therefore not be possible for a person skilled in the art to predict that these compounds would prevent a metal ion from binding specifically to a histidine residue in this region.

Citation 6

The claims are novel and inventive in light of this citation. Page 767, left hand side, last 8 lines states that nicotine binds to the His13 and His14 of Aβ , preventing β-amyloid precipitation. The binding of nicotine to these histidine residues is likely to be relatively weak and it would therefore be unlikely to compete with metal ion binding to these sites. Without evidence to the contrary, it would therefore appear that nicotine would not act as a compound that would inhibit the binding of one or more metal ions to at least one histidine residue within the N-terminal loop of the β-amyloid peptide and therefore the claims are novel and inventive.

Citation 7

The claims are novel and inventive in light of this citation. Page 141 paragraph 2 discloses antibodies which bind at the N-terminus of Aβ. It does not however disclose that these synthetic antibodies specifically bind at the His6 site and it cannot therefore be said that a metal ion would definitely be inhibited from binding at this histidine residue.

Citation 8

The claims are novel and inventive in light of this citation. This document discloses that melatonin inhibits Aβ aggregation through binding at the N-terminus of the peptide. The binding site is disclosed to directly involve His6, 13 and 14 and an Asp residue. However there is no evidence in this citation that melatonin would bind strongly enough to prevent metal ions from binding at the histidine residues, or that melatonin would displace metal ions already bound at the N-terminal loop. Without evidence to the contrary, it would appear that melatonin would not necessarily bind to at least one histidine residue in the N-terminal loop of Aβ such that the binding of one or more metal ions is inhibited.

Supplemental Box
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Continuation of V

Citation 9

The claims are novel and inventive in light of this citation. This citation discloses antibodies that bind to the N-terminus of Aβ. It does not however disclose that these antibodies specifically bind to at least one histidine residue within the N-terminus. It cannot therefore be said that these antibodies would inherently inhibit the binding of one or more metal ions to one of the N-terminal loop histidine residues.

pyrocarbonate, which binds to the imidazole nitrogen of histidine (Atwood et al., 1998). Subsequently to the priority date of this application, it was reported that three histidine residues in the N-terminal hydrophilic region of human Aβ provide primary metal binding sites, and that the solubility of the complex between metal and Aβ depends on the mode of metal binding. The authors proposed that Cu^{2+} would protect Aβ against Zn-induced aggregation by competing with zinc ions for binding sites on the histidine residues (Miura et al., 2000).

In contrast, we propose that inhibition of binding of zinc, copper and/or iron to the Aβ peptide will have significant therapeutic value in the treatment of Alzheimer's disease.

It has been reported that certain tetrapyrroles, especially certain porphyrin and phthalocyanine compounds inhibit conversion of normal, protease-sensitive prion protein (PrPsen) to the protease-resistant form (PrPres) which is implicated in the pathogenesis of transmissible spongiform encephalopathies (TSEs) such as Creutzfeldt-Jacob disease (Caughey et al., 1998), and that three of these compounds inhibited TSE disease *in vivo* (Priola et al., 2000). However, both metal-free and metal-complexed tetrapyrroles were active, and the authors considered that the mechanism of action involved direct interaction between the compound and the infectious agent. Although the authors speculated that the compounds might also be useful in the treatment of non-prion mediated amyloid-related conditions, such as Alzheimer's disease or Type II diabetes, this was no more than speculation (Priola et al., 2000). Moreover, all of the compounds disclosed have multiple substitutions or the tetrapyrrole ring, whereas the tetrapyrrole compounds of the present invention are preferably substituted only on one of the rings.

It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of

wherein the core molecule has a conformation and polarity such that the acid group(s) interact with one of more of His6, His13 and His14.

9. A compound according to claim 8, in which the acid group is selected from the group consisting of CO_2H, PO_3H_2, SO_3H, OSO_3H_2, and OPO_3H_2.

10. A compound according to claim 9, which is a molecule with one to three carboxylic acid groups, the length of the molecule being such that it can be received within the N-terminal loop, and such that at least one carboxyl group is in proximity to at least one of the histidine residues.

11. A compound according to any one of claims 1 to 10, which is an organic molecule, a peptide or a metal complex.

12. A compound according to claim 9, which is not a metal complex.

13. A compound according to claim 9, which has overall hydrophobic character.

14. A compound according to claim 10, which is able to penetrate the blood-brain barrier.

15. A compound according to any one of claims 1 to 14, which comprises, or is conjugated to, a targeting moiety.

16. A compound according to claim 15, in which the targeting moiety is selected from the group consisting of polypeptides, nucleic acids, carbohydrates, lipids, β-amyloid ligands, antibodies, and dyes.

17. A compound according to claim 15, in which the targeting moiety has a hydrophobic region which interacts with the tail of the β-amyloid peptide.

18. A compound according to claim 17, in which the targeting moiety comprises a fatty acid molecule.

19. A compound according to any one of claims 15 to 18, in which the targeting moiety targets the compound to the site defined by residues 15-21 of the β-amyloid peptide.

20. A compound according to claim 17, in which the targeting moiety is a peptide which comprises a sequence which corresponds to that of residues 15-21 of the β-amyloid peptide.

21. A compound according to any one of claims 15 to 20, in which the inhibitor-targeting moiety complex is able to penetrate the blood-brain barrier.

22. A method of selecting or designing a compound which inhibits the binding of metal ions to the N-terminal loop of the β-amyloid peptide, which method comprises the steps of

(i) selecting or designing a compound which has a conformation and polarity such that it binds to at least one amino acid in the N-terminal loop selected from the group consisting of His6, His 13 and His14; and

(ii) testing the compound for the ability to inhibit binding of metal ions to the N-terminal loop of the β-amyloid peptide.

23. A method according to claim 22, in which the compound binds to at least two histidine residues in the N-terminal loop.

24. A method according to claim 23, in which the compound binds to at least three histidine residues in the N-terminal loop.

25. A method according to any one of claims 22 to 24, in which the compound also binds to at least one additional amino acid in the N-terminal loop, selected from the group consisting of Asp7, Tyr10, and Glu11.

26. A method according to claim 26, in which the compound inhibits binding of Cu^{2+}, Zn^{2+} and Fe^{3+} ions, but not Mg^{2+} or Ca^{2+} ions.

27. A method according to any one of claims 22 to 26, in which the compound has overall hydrophobic character.

28. A method according to claim 27, in which the compound is able to penetrate the blood-brain barrier.

29. A compound which inhibits the binding of metal ions to the N-terminal loop of the β-amyloid peptide, wherein

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NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

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509 St Kilda Road
Melbourne, VIC 3004
AUSTRALIE

Date of mailing (day/month/year) 22 November 2000 (22.11.00)	
Applicant's or agent's file reference VS:FP13136	**IMPORTANT NOTIFICATION**
International application No. PCT/AU00/00886	International filing date (day/month/year) 21 July 2000 (21.07.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 23 July 1999 (23.07.99)
Applicant BIOMOLECULAR RESEARCH INSTITUTE LTD et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

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Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
23 July 1999 (23.07.99)	PQ 1804	AU	08 Augu 2000 (08.08.00)

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